DETAILED ACTION

Formal Matters

Applicants' response and amendments to the claims, filed 7/1/2009, are acknowledged and entered. Claims 22, 26-28, and 32-34 are pending and under examination.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 7/1/2009 has been entered.

Claim Interpretation

Claim 22 is the only independent claim presented for examination. Claim 22 recites a "kit" for carrying out the combined administration of suramin with one or more cytotoxic agents, comprising:

(a) suramin formulated in a pharmaceutical carrier;

(b) a cytotoxic agent being one or more of an anti-microtubule agent, a topoisomerase I inhibitor, a topoisomerase II inhibitor, an anti-metabolite, a mitotic inhibitor, an alkylating agent, an intercalating agent, an agent capable of interfering with a signal transduction pathway, an agent that promotes one or more of apoptosis or necrosis, an interferon, an interleukin, or a tumor necrosis factor, or radiation; and

(c) instructions for therapeutic use of said suramin in combination with said cytotoxic agent(s) in one or more of inhibiting growth, proliferation of tumor cells, or inducing killing of tumor cells.

The recited “instructions” delineate how suramin and the chemotherapeutic agent are *intended to be administered*, including a method of determining at what dose suramin should be administered so as to establish a low circulating dose of suramin in a patient of below about 200

μM. As such, the recited instructions merely disclose an intended use of the claimed composition and instructions for administering suramin.

Upon careful review of the claims, Applicant's previous arguments, and guidance provided in the MPEP and established case law, the Examiner is not persuaded that the claimed instructions breath "life and meaning" into the claimed composition. The instructions have no bearing whatsoever on the claimed suramin and cytotoxic agents present in the composition and further do not affect the amounts of suramin or cytotoxic agent present in the kit. For example, the claims reasonably encompass a vat of suramin and cytotoxic agent. The recited instructions would only indicate to the skilled artisan how to determine how much suramin to remove from the vat and administer to a patient but do not in any way limit the amount of suramin present in the claimed kit.

As clearly set forth in the MPEP and established case law, instructions reciting an intended use or printed material not functionally related to the product are not to be given patentable weight by the Examiner when examining the patentability of compositions or kits comprising active agents. MPEP 2112.01 (III) states that where the only difference between a prior art product and a claimed product is printed matter that is not functionally related to the product, the content of the printed matter will not distinguish the claimed product from the prior art. Also see *In re Ngai*, 367 F.3d 1336, 1339, 70 USPQ2d 1862, 1864 (Fed. Cir. 2004) and *In re Gulack*, 703 F.2d 1381, 1385-86, 217 USPQ 401, 404 (Fed. Cir. 1983).

In this case, the recited instructions (*i.e.*, printed material) are not functionally related to the claimed kit (*i.e.*, product) because the instructions do not determine what is present in the composition or how much suramin or cytotoxic agent is present in the kit. The printed material only establishes *how to administer suramin* so as to establish a low circulating dose of suramin in a patient of below about 200 μM. Contrary to Applicant's assertions, the claimed nomogram is not required to enable use of a kit comprising suramin and a cytotoxic agent. One skilled in the art could readily administer any known therapeutic dose of suramin and any known therapeutic dose of a cytotoxic agent to treat cancer and does not require Applicant's instructions and nomogram to do so. Applicants are respectfully reminded that the present claims are drawn to a **product**, not a method of treatment.

Claim Rejections - 35 USC § 101 – New Ground of Rejection

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 32-34 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claims 32-34 depend from the "kit" of claim 22. The kit of claim 22 is a product comprising suramin, a cytotoxic agent, and instructions "calling for" administering suramin and a cytotoxic agent. However, claims 32-34 recite active method steps, *e.g.*, "..a suramin dose *is administered*..."; a concentration of suramin "...*is achieved* in a patient"; "...suramin *is given*..."; "...suramin *is administered to a patient*..."; and "...a chemotherapeutic agent thereafter *is administered* to said patient....". The claims are thus non-statutory because they depend from a product claim but recite active method steps. While the instructions of claim 22 call for administering suramin and a cytotoxic agent (*i.e.*, provide instructions for administration), claims 32-34 require administration of suramin and/or cytotoxic agent and thus are drawn both to a product and a method.

Claim Rejections - 35 USC § 112 – 2nd Paragraph - New Ground of Rejection

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 22, 26-28, and 32-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 22 recites the limitation "said chemotherapeutic agent" in line 16. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103 – New Grounds of Rejection

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 22, 26-28, and 32-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Agyin *et al***. (USP No. 6,900,235; Issued May 31, 2005; Filed Sep. 29, 2000).

Agyin *et al*. disclose benzimidazole compounds for the treatment of cancers (Abstract; col. 2, line 39 to col. 3, line 61). The benzimidazole compounds are inhibitors of microtubules as recited in claim 22 (col. 25, lines 43-67; Table 5). The compounds of the invention are disclosed to be useful in combination therapy, such as by combining the benzimidazole compound with a chemotherapeutic agent and/or "potentiator" (col. 17, lines 1-60; col. 23, lines 29-31). A suitable potentiator is suramin as recited in claim 22 (col. 17, lines 56-57).

Agyin *et al*. disclose pharmaceutical kits for the treatment of cancer comprising one or more containers containing a pharmaceutical composition comprising a compound of the invention, pharmaceutically acceptable carriers, and instructions, *e.g*., printed instructions either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components (col. 24, lines 7-22).

With regard to claim 26, Agyin *et al*. teach that carboplatin is a chemotherapeutic agent that may be combined with the disclosed anti-microtubule compounds (Table 3A) and that the compounds of the invention can be combined with chemotherapeutic agents **and**/or potentiators to provide combination therapy (col. 23, lines 29-31). Accordingly, addition of both suramin and carboplatin to a kit comprising an anti-microtubule compound as disclosed in Agyin *et al*. would have been obvious to one skilled in the art at the time the invention was made.

Accordingly, it would have been *prima facie* obvious to one of ordinary skill in the art to formulate a kit comprising suramin as a potentiator and an anti-microtubule agent as disclosed in Agyin *et al.* for the treatment of cancer. One skilled in the art would have been motivated to additionally provide instructions for the therapeutic use of a suramin potentiator in combination with an anti-microtubule agent of Agyin *et al.* As discussed in previous Office Actions, there must be a functional relationship between the printed matter and a substrate in order for printed material to have any patentable weight.

With regard to claims 27-28 and 32-34, in view of the guidance provided in the MPEP and the court decisions in *Gulack* and especially *Ngai*, it is the position of the Examiner that the instantly claimed instructions for using suramin in combination with cytotoxic agents do not provide a functional relationship between the printed matter and the claimed product and thus are not given patentable weight. All the printed matter does is teach how to administer suramin to achieve a circulating concentration of below about 200 μM in a patient. Claim 27-28 and 32-34 only further limit the instructions, not the recited kit.

Response to Arguments

Applicants argue that Agyin provides limited data to support enablement for the treatment of cancers. This argument is not persuasive because the claims are not drawn to a method of treatment and the rejection of record is not made on the basis of treating cancer. Rather, Agyin motivates one skilled in the art to combine a benzimidazole anticancer agent disclosed therein with a potentiator such as suramin and additional anticancer agents in a kit as recited in the instant claims.

Secondly, Applicants argue that Agyin does not teach a suramin combination. The fact that there are other possible combinations suggested by Agyin is not pertinent to the present rejection because it would be routine for the skilled artisan to combine a benzimidazole compound disclosed in Agyin with ANY chemotherapeutic agent. Further, the claims are not limited to any particular cytotoxic agents and are thus also drawn to an unlimited number of possible combinations of suramin with other cytotoxic agents.

Thirdly, Applicants argue that Agyin does not teach using suramin as a potentiator. This is not persuasive because the claims are not limited to kits containing a particular amount of

suramin or cytotoxic agent. The fact that Applicants found that suramin leads to sensitization only at lower doses is not pertinent to the patentability of the claimed KITS. Applicants predicate patentability of their claimed kits on the nomogram that is required to enable the use of the kit containing suramin. Applicants allege that the inventive element of the instructions that enable application of medicaments and that provide a functional relationship between printed matter and the claimed kit. This is not persuasive because the instructions do not control what is IN the kit as discussed above. Put another way, the recited instructions have no bearing and place no limitations on the components of the kit or the content of the kit. Rather, the instructions only tell one skilled in the art *how to administer* the components of the kit in a particular manner. As such, there is not a functional relationship between the instructions and the claimed kit. There can be no doubt that the skilled artisan could administer suramin and a cytotoxic agent in a manner distinct from that disclosed in Applicant's recited instructions. However, such administration does not depend on the contents or amounts present in the kit.

If the Office were to accept Applicant's arguments, inventors could theoretically patent a multitude of kits containing suramin and a cytotoxic agent that differ only in the content of the instructions. For example, it would be possible, using Applicant's rationale, to patent two kits containing suramin and paclitaxel, wherein one kit contains the claimed nomogram for determining the dose of suramin required to establish a circulating concentration of suramin in a patient of below about 200 μM and another kit contains a different set of administration instructions establishing a circulating concentration of suramin of above 200 μM. A third kit containing an even different set of administration instructions could also be theoretically patented. The number of possible kits, containing the SAME active agents could theoretically be patented based ONLY on a difference in the instructions for administration of the active agents. This is clearly what the court in *Ngai* was seeking to avoid when they said, "If we were to adopt Ngai's position, anyone could continue patenting a product indefinitely provided that they add a new instruction sheet to the product. This was not envisioned by Gulack".

Claims 22, 27-28, and 32-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Tu *et al***. (Clinical Cancer Research, May 1998, vol. 4, pages 1193-1201) in view of **Agyin *et al***. (USP No. 6,900,235; Issued May 31, 2005; Filed Sep. 29, 2000).

Tu *et al*. disclose that suramin combined with doxorubicin is effective in the treatment of patients with androgen-independent prostate cancer (Abstract). The authors disclose that suramin is an agent with diverse biological effects that result in tumor suppression with cytotoxic effects including activation of apoptotic cell death, inhibition of cellular energy metabolism, and inhibition of DNA and RNA polymerases, protein kinase C, and DNA topoisomerase II (page 1193, right column). The most serious toxicities of suramin are dose dependent and occur when plasma suramin levels exceed 350 μg/mL.[1] Suramin was known to have synergistic antitumor activity when combined with doxorubicin (page 1193, right column). Doxorubicin is an antitumor antibiotic whose mechanism of action is believed to involve the formation of free radicals and the inhibition of topoisomerase II, causing DNA damage (*id*.). Doxorubicin is a cytotoxic agent encompassed by the instant claims.

The authors provide instructions for administering suramin and doxorubicin to patients to treat prostate cancer and provide measurements of suramin plasma concentrations (pages 1194-1195; Table 3). Tu *et al*. specifically disclose adjusting suramin doses proportionately based on assessment of steady-state plasma concentrations of suramin (page 1194, right column). As seen in Table 3, the circulating plasma concentrations of suramin are below about 200 μM as recited in the instantly claimed instructions. In fact, the authors disclose that single-agent suramin has a narrow clinical therapeutic index of 150 to 250 μg/mL (page 1199, left column). 150 to 250 μg/mL suramin is equivalent to 105 to 175 μM suramin, which is below the amount recited in the claimed instructions.

The authors conclude that the results from this study could be used to develop future clinical studies of suramin combined with other chemotherapeutic agents in the treatment of prostate cancer and that long-term exposure to suramin at lower concentrations and in combination with other chemotherapeutic agents should be explored. The authors explicitly

[1] The molecular weight of suramin is 1429.21 g/mol. 350 μg/mL is equivalent to about 245 μM.

suggest a fixed dosing scheme targeting a suramin concentration of 200 μg/mL (*i.e.*, 140 μM) for future suramin combination studies (page 1200, right column).

Tu *et al.* differ from the instant claims in that they do not explicitly disclose a "kit" comprising suramin and doxorubicin and instructions for administration.

However, providing therapeutically active agents in kits with instructions for administration of the active agents is routine in the art of medicine. The skilled artisan is aware of the benefits of such kits, such as ease of transport, storage, and distribution. For example, Agyin *et al.* disclose pharmaceutical kits for the treatment of cancer comprising one or more containers containing a pharmaceutical composition comprising a compound of the invention, pharmaceutically acceptable carriers, and instructions, *e.g.*, printed instructions either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components (col. 24, lines 7-22).

As such, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to formulate a kit comprising suramin and doxorubicin as suggested and motivated by Tu *et al.* for use in the treatment of prostate cancer. Using the disclosure of Tu et al. as a guide, the skilled artisan could readily provide instructions for administering suramin and doxorubicin to treat prostate cancer, wherein the dose of suramin administered is such that a therapeutic, non-toxic concentration of suramin is provided to the patient. Tu *et al.* disclose that single-agent suramin has a narrow clinical therapeutic index of 150 to 250 μg/mL (*i.e.*, 105 to 175 μM) and explicitly suggest a fixed dosing scheme targeting a suramin concentration of 200 μg/mL (*i.e.*, 140 μM). Agyin *et al.* disclose that it is well-known and routine in the art to provide therapeutic agents in pharmaceutical kits comprising a therapeutic agent(s), pharmaceutically acceptable carriers, and instructions, *e.g.*, printed instructions either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components.

With regard to claims 27-28 and 32-34, in view of the guidance provided in the MPEP and the court decisions in *Gulack* and especially *Ngai*, it is the position of the Examiner that the instantly claimed instructions for using suramin in combination with cytotoxic agents do not provide a functional relationship between the printed matter and the claimed product and thus are

not given patentable weight. All the printed matter does is teach how to administer suramin to achieve a circulating concentration of below about 200 μM in a patient. Claim 27-28 and 32-34 only further limit the instructions, not the recited kit. Regardless of this fact, as discussed above, Tu et al. provide guidance and direction to administer suramin in such a way so as to provide a circulating concentration of suramin below 200 μM.

Claims 22, 27-28, and 32-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Klohs *et al.*** (USP No. 5,597,830; Issued Jan. 28, 1997) in view of **Agyin *et al.*** (USP No. 6,900,235; Issued May 31, 2005; Filed Sep. 29, 2000).

Klohs et al. disclose suramin in combination with a vinca alkaloid or estramustine is synergistic for treating cancer (Abstract). Compositions for use in the invention consist essentially of suramin and a vinca alkaloid or estramustine together with common excipients, diluents, and carriers (col. 1, line 65 to col. 2, line 10). Suramin is disclosed to be administered at doses from about 275 mg/m^2 to about 1000 mg/m^2 and ideally is administered at a dose to provide plasma levels of about 100 to about 300 μg/mL (*i.e.*, about 70 μM to about 210 μM) (col. 2, lines 27-35). The inventors disclose a combination comprising each active ingredient packaged separately, wherein the individually packaged drugs can be placed in a single carton, thereby providing convenience to the attending physician or medical attendant (*i.e.*, a kit) (col. 4, lines 39-44).

Klohs *et al.* differ from the instant claims in that they do not explicitly disclose a kit comprising suramin and a vinca alkaloid or estramustine and instructions for administration.

However, providing therapeutically active agents in kits with instructions for administration of the active agents is routine in the art of medicine. The skilled artisan is aware of the benefits of such kits, such as ease of transport, storage, and distribution. Klohs *et al.* disclose that kits comprising the individual active agents provide convenience to physicians or medical attendants. Agyin *et al.* disclose pharmaceutical kits for the treatment of cancer comprising one or more containers containing a pharmaceutical composition comprising a compound of the invention, pharmaceutically acceptable carriers, and instructions, *e.g.*, printed instructions either as inserts or as labels, indicating quantities of the components to be

administered, guidelines for administration, and/or guidelines for mixing the components (col. 24, lines 7-22).

As such, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to formulate a kit comprising suramin and a vinca alkaloid or estramustine as suggested and motivated by Klohs *et al.* for use in the treatment of cancer. Using the disclosure of Klohs *et al.* as a guide, the skilled artisan could readily provide instructions for administering suramin and a vinca alkaloid or estramustine to treat cancer, wherein the dose of suramin administered is such that a therapeutic, non-toxic concentration of suramin is provided to the patient. Klohs *et al.* disclose that suramin is to be administered at doses from about 275 mg/m^2 to about 1000 mg/m^2 and ideally is administered at a dose to provide plasma levels of about 100 to about 300 μg/mL (*i.e.*, about 70 μM to about 210 μM) (col. 2, lines 27-35). The inventors disclose a kit comprising each active ingredient packaged separately wherein the individual packages can be placed in a single carton. Agyin *et al.* disclose that it is well-known and routine in the art to provide therapeutic agents in pharmaceutical kits comprising a therapeutic agent(s), pharmaceutically acceptable carriers, and instructions, *e.g.*, printed instructions either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components.

With regard to claims 27-28 and 32-34, in view of the guidance provided in the MPEP and the court decisions in *Gulack* and especially *Ngai*, it is the position of the Examiner that the instantly claimed instructions for using suramin in combination with cytotoxic agents do not provide a functional relationship between the printed matter and the claimed product and thus are not given patentable weight. All the printed matter does is teach *how* to administer suramin to achieve a circulating concentration of below about 200 μM in a patient. Claim 27-28 and 32-34 only further limit the instructions, not the recited kit. Regardless of this fact, as discussed above, Klohs et al. provide guidance and direction to administer suramin in such a way so as to provide suramin plasma levels of about 100 to about 300 μg/mL (*i.e.*, about 70 μM to about 210 μM).

Claims 22, 26-28, and 32-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Lopez *et al.*** (European Journal of Cancer, 1994, vol. 30A, no. 10, pages 1545-1549) in

view of **Klohs *et al.*** (USP No. 5,597,830; Issued Jan. 28, 1997) and **Agyin *et al.*** (USP No. 6,900,235; Issued May 31, 2005; Filed Sep. 29, 2000).

Lopez *et al.* disclose that suramin has shown antitumor activity *in vitro* and *in vivo* and that at plasma levels higher than 200 μM there is excessive toxicity (Abstract). Lopez *et al.* sought to improve the antitumor effects of suramin by combining it with several other antitumor agents. In this regard, the authors demonstrate that suramin in combination with doxorubicin, 5-fluorouracil, cisplatin, or tumor necrosis factor resulted in synergistic growth inhibition of breast and/or prostate cancer cells (Abstract; Table 2).

The instant claims differ from Lopez *et al.* in that the primary reference does not disclose kits comprising suramin and the other chemotherapeutic agents.

However, Klohs *et al.* disclose suramin in combination with a vinca alkaloid or estramustine is synergistic for treating cancer (Abstract). Suramin is disclosed to be administered at doses from about 275 mg/m^2 to about 1000 mg/m^2 and ideally is administered at a dose to provide plasma levels of about 100 to about 300 μg/mL (*i.e.*, about 70 μM to about 210 μM) (col. 2, lines 27-35). The inventors disclose a combination comprising each active ingredient packaged separately, wherein the individually packaged drugs can be placed in a single carton, thereby providing convenience to the attending physician or medical attendant (*i.e.*, a kit) (col. 4, lines 39-44).

The instant claims differ from Klohs *et al.* in that the secondary reference does not teach kits with instructions for administration.

However, providing therapeutically active agents in kits with instructions for administration of the active agents is routine in the art of medicine. The skilled artisan is aware of the benefits of such kits, such as ease of transport, storage, and distribution. Klohs *et al.* disclose that kits comprising the individual active agents (*e.g.*, suramin and a cytotoxic agent) provide convenience to physicians or medical attendants. Agyin *et al.* disclose pharmaceutical kits for the treatment of cancer comprising one or more containers containing a pharmaceutical composition comprising a compound of the invention, pharmaceutically acceptable carriers, and instructions, *e.g.*, printed instructions either as inserts or as labels, indicating quantities of the

components to be administered, guidelines for administration, and/or guidelines for mixing the components (col. 24, lines 7-22).

As such, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to formulate a kit comprising suramin and doxorubicin, 5-fluorouracil, cisplatin, or tumor necrosis factor as suggested and motivated by Lopez *et al.* in view of Klohs *et al.* for use in the treatment of cancer. Using the disclosures of Lopez *et al.* and Klohs *et al.* as a guide, the skilled artisan could readily provide instructions for administering suramin and doxorubicin, 5-fluorouracil, cisplatin, or tumor necrosis factor to treat cancer, wherein the dose of suramin administered is such that a therapeutic, non-toxic concentration of suramin is provided to the patient. Lopez et al. teach that plasma levels above 200 μM, suramin results in "excessive toxicity", thus motivating one skilled in the art to administer suramin in doses so as not to exceed a plasma level above 200 μM. Klohs *et al.* provide such guidance, disclosing that suramin is to be administered at doses from about 275 mg/m^2 to about 1000 mg/m^2 and ideally is administered at a dose to provide plasma levels of about 100 to about 300 μg/mL (*i.e.*, about 70 μM to about 210 μM) (col. 2, lines 27-35). Klohs *et al.* disclose a kit comprising each active ingredient packaged separately wherein the individual packages can be placed in a single carton. The skilled artisan could readily and routinely modify the kits of Klohs et al. so as to provide kits comprising suramin and other cytotoxic agents, such as doxorubicin, 5-fluorouracil, cisplatin, or tumor necrosis factor as suggested and motivated by Lopez *et al.* Agyin *et al.* disclose that it is well-known and routine in the art to provide therapeutic agents in pharmaceutical kits comprising a therapeutic agent(s), pharmaceutically acceptable carriers, and instructions, *e.g.*, printed instructions either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components.

With regard to claims 27-28 and 32-34, in view of the guidance provided in the MPEP and the court decisions in *Gulack* and especially *Ngai*, it is the position of the Examiner that the instantly claimed instructions for using suramin in combination with cytotoxic agents do not provide a functional relationship between the printed matter and the claimed product and thus are not given patentable weight. All the printed matter does is teach *how* to administer suramin to

achieve a circulating concentration of below about 200 μM in a patient. Claim 27-28 and 32-34 only further limit the instructions, not the recited kit. Regardless of this fact, as discussed above, both Lopez *et al.* and Klohs *et al.* provide guidance and direction to administer suramin in such a way so as to provide suramin plasma levels of below about 200 μM (Lopez *et al.*) or about 100 to about 300 μg/mL (*i.e.*, about 70 μM to about 210 μM) (Klohs *et al.*).

Regarding the above rejections under 35 U.S.C. 103, it is noted that the MPEP and established case law supports the rejection of pharmaceutical kits that differ from the prior art only in the content of the provided instructions. The following section of the M.P.E.P., as noted by Applicants in their response filed 9/10/2007 (page 7) is deemed relevant to the present claims:

> "Where the only difference between a prior art product and a claimed product is printed matter that is not functionally related to the product, the content of the printed matter will not distinguish the claimed product from the prior art. *In re Ngai*, 367 F.3d 1336, 1339, 70 USPQ2d 1862, 1864 (Fed. Cir. 2004) (Claim at issue was a kit requiring instructions and a buffer agent. The Federal Circuit held that the claim was anticipated by a prior art reference that taught a kit that included instructions and a buffer agent, even though the content of the instructions differed.). See also *In re Gulack*, 703 F.2d 1381, 1385-86, 217 USPQ 401, 404 (Fed. Cir. 1983) ("Where the printed matter is not functionally related to the substrate, the printed matter will not distinguish the invention from the prior art in terms of patentability .... [T]he critical question is whether there exists any new and unobvious functional relationship between the printed matter and the substrate.")." M.P.E.P. § 2112.01

The decision in *Gulack* held that there must be a functional relationship between the printed matter and a substrate in order for printed material to have any patentable weight. However, in *Ngai*, the court distinguished claims directed to a kit comprising instructions and a buffer (more closely related to the present case) from the printed band and instructions at issue in *Gulack*. There the printed matter and the circularity of the band were interrelated, so as to produce a new product useful for "educational and recreational mathematical" purposes. In *Ngai*, addition of a new set of instructions into a known kit was held to not interrelate with the kit in the same way as the numbers interrelated with the band. In *Gulack*, the printed matter would not achieve its educational purposes without the band, and the band without the printed matter would similarly be unable to produce the desired result. In the present case, the printed matter in no way depends on the kit (*i.e.*, a kit containing suramin formulated in a pharmaceutical carrier

and a cytotoxic agent), and the kit does not depend on the printed matter (*i.e.*, instructions for administering suramin in combination with cytotoxic agents). All that the printed matter does is teach a method of administering an obvious product. As the court stated in *Ngai*, "If we were to adopt Ngai's position, anyone could continue patenting a product indefinitely provided that they add a new instruction sheet to the product. This was not envisioned by *Gulack*. Ngai is entitled to patent his invention of a new RNA extraction method, and the claims covering that invention were properly allowed. He is not, however, entitled to patent a known product by simply attaching a set of instructions to that product." (Emphasis added).

In the instant case, the cited prior art clearly teaches, suggests, and motivates one skilled in the art to formulate pharmaceutical compositions and kits comprising suramin and other cytotoxic agents for the treatment of cancer. It was clearly known in the art that suramin has antitumor activity, is synergistic when combined with other chemotherapeutic agents, and results in excessive toxicity when plasma levels of suramin are greater than 200 μM. As such, it would be obvious to one skilled in the art to formulate suramin in a kit with other cytotoxic agents, especially those which were known to be synergistic when administered with suramin, and to provide instructions for treating cancer with the active agents in the kit. It would further have been obvious to the skilled artisan to instruct those administering suramin not to administer doses that result in plasma concentrations above 200 μM which cause excessive toxicity. As discussed above, the claimed instructions do not control what is in the kit. Put another way, the recited instructions have no bearing and place no limitations on the components of the kit, the content of the kit, or the amounts of active agents in the kit. The kit, in and of itself, stands alone and does not require the claimed instructions to "breath life and meaning" into the kit. Rather, the instructions only tell one skilled in the art *how to administer* the components of the kit in a particular manner. As such, there is not a functional relationship between the instructions and the claimed kit. There can be no doubt that the skilled artisan could administer suramin and a cytotoxic agent in a manner distinct from that disclosed in Applicant's recited instructions. However, even such a distinct administration method does not change the contents of the kit or the amounts of active agents present in the kit.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James D Anderson/
Examiner, Art Unit 1614